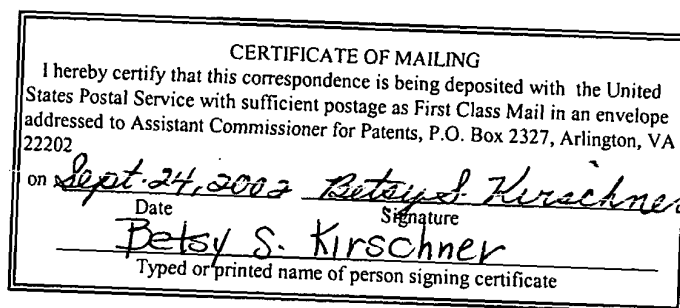


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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jordan J.N. Tang and Arun K. Ghosh  
Application No.: 09/603,713 Group Art Unit: 1653  
Filed: June 27, 2000 Examiner: Abdel A. Mohamed  
Title: Inhibitors of Memapsin 2 and Use Thereof



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FIFTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents  
P.O. Box 2327  
Arlington, VA 22202

Sir:

This Information Disclosure Statement is submitted:

☐ under 37 CFR 1.129(a), or  
(First/Second submission after Final Rejection)

☐ under 37 CFR 1.97(b), or  
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits in a non-provisional application, including a CPA, or a Request for Continued Examination).

☒ under 37 CFR 1.97(c) together with either:  
☐ a Statement under 37 CFR 1.97(e), as checked below, or  
☒ a \$180.00 fee under 37 CFR 1.17(p), or  
(After the 37 CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)

☐ under 37 CFR 1.97(d) together with:  
☐ a Statement under 37 CFR 1.97(e), as checked below, and  
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(Filed after final action or notice of allowance, whichever occurs first, but on or before payment of the issue fee)

☐ under 37 CFR 1.97(i):  
Applicant requests that the IDS and cited reference(s) be placed in the application filewrapper.  
(Filed after payment of issue fee)

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10/01/2002 MKCJW1 09603713 15000000

Statement Under 37 CFR 1.97(e)

- ☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or
- ☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)

Applies to original applications (other than design) filed on or after May 29, 2000

- ☐ Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

☒ Enclosed herewith is form PTO-1449:

- ☒ Copies of the cited references (AJ-AK, AA2-AE2, AP-AQ, AL2-AQ2, AL3-AQ3, AL4, AW-AZ, AR2-AZ2, AR3-AZ3, AR4-AZ4, AR5-AZ5, AR6-AZ6, AR7-AZ7, AR8-AZ8, AR9-AZ9, AR10-AZ10 and AR11-AX11) are enclosed.
- ☐ Copies of cited references are enclosed except those entered in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed. [The earlier application contains copies of the cited references.]
- ☐ The listed references were cited in the enclosed International Search Report in a counterpart foreign application.
- ☐ The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:
- ☐ the explanation provided on the attached sheet.
  - ☐ the explanation provided in the Specification.
  - ☐ submission of the enclosed International Search Report.
  - ☐ submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
  - ☐ the enclosed English language abstract.

☐ Applicant requests that the following non-published pending applications be considered:

Examiner's  
Initials

\_\_\_\_ U.S. Patent Application No. [ ], by [inventor(s)], filed [ ], Docket No.: [ ]  
\_\_\_\_ U.S. Patent Application No. [ ], by [inventor(s)], filed [ ], Docket No.: [ ]  
\_\_\_\_ U.S. Patent Application No. [ ], by [inventor(s)], filed [ ], Docket No.: [ ]

\_\_\_\_\_  
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It is requested that the information disclosed herein be made of record in this application.

Method of payment:

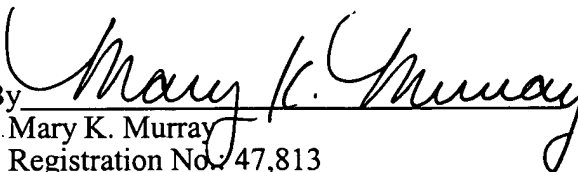
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☐ Please charge Deposit Account 08-0380 in the amount of \$[ ]. A copy of this Statement is enclosed.

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Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By   
Mary K. Murray

Registration No. 47,813

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: *September 24, 2002*

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application No.: 09/603,713 Group Art Unit: 1653  
Filed: June 27, 2000 Examiner: Abdel A. Mohamed  
Title: Inhibitors of Memapsin 2 and Use Thereof



CERTIFICATE OF MAILING	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202	
on <u>Sept. 24, 2002</u>	<u>Betsy S. Kirschner</u>
Date	Signature
<u>Betsy S. Kirschner</u>	
Typed or printed name of person signing certificate	

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\_\_\_\_ U.S. Patent Application No. [ ], by [inventor(s)], filed [ ], Docket No.: [ ]

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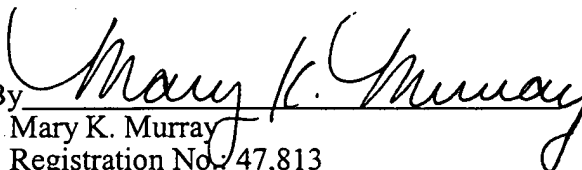
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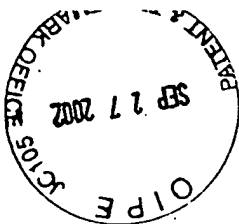
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Dated: *September 24, 2002*



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PTO-1449 REPRODUCED  <b>5<sup>TH</sup> SUPPLEMENTAL INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b>  September 24, 2002  (Use several sheets if necessary)				ATTORNEY DOCKET NO. 2932.1008-000		APPLICATION NO. 09/603,713	
				APPLICANT Jordan J.N. Tang and Arun K. Ghosh			
				FILING DATE June 27, 2000		GROUP 1653	
<b>U.S. PATENT DOCUMENTS</b>							
EXAM- INER INI- TIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE IF APPROPRIATE
	AJ	5,200,339	04/06/93	Abraham	435	212	
	AK	5,733,768	03/31/98	Dixon et al.	435	226	
	AA2	5,942,400	08/24/99	Anderson et al.	435	7.1	
	AB2	5,978,740	11/02/99	Armistead et al.	702	19	
	AC2	5,986,054	11/16/99	George-Hyslop et al.	530	350	
	AD2	6,420,534 B1	07/16/01	Gurney et al.	530	827	
	AE2	6,077,682	06/20/00	Inouye et al.	435	15	
<b>FOREIGN PATENT DOCUMENTS</b>							
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION YES NO
	AP	WO 96/40885 A2	19 DEC 96	PCT			
	AQ	WO 97/27296 A1	31 JUL 97	PCT			
	AL2	WO 98/13488 A2	2 APR 98	PCT			
	AM2	WO 98/15828 A1	16 APR 98	PCT			
	AN2	WO 98/21589 A1	22 MAY 98	PCT			
	AO2	WO 98/26059 A1	18 JUN 98	PCT			
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>							
	AW	Abad-Zapatero, C. et al., "Structure of a secreted aspartic protease from C. albicans complexed with a potent inhibitor: implications for the design of antifungal agents," <i>Protein Sci</i> 5(4):640-52 (1996).					
EXAMINER				DATE CONSIDERED			



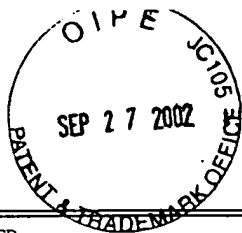
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Page 2 of 9

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		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES NO
	AP2	WO 99/51752 A1	14 OCT 99	PCT			
	AQ2	WO 99/64587 A1	16 DEC 99	PCT			
	AL3	WO 00/17369 A2	30 MAR 00	PCT			
	AM3	WO 00/23576 A2	27 APR 00	PCT			
	AN3	WO 00/47618 A2	17 AUG 00	PCT			
	AO3	WO 00/58479 A1	05 OCT 00	PCT			
	AP3	WO 00/77030 A1	21 DEC 00	PCT			
	AQ3	EP 0 855 444 A2	20 JUL 98	EPO			
	AL4	JP 10 108 681	28 APR 98	JP			
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>							
	AX	Abbenate, G., et al., "Inhibitors of $\beta$ -Amyloid Formation Based on the $\beta$ -Secretase Cleavage Site," <i>Biochemical and Biophysical Research Communications</i> 268(1):133-135 (2000).					
	AY	Adams, M.D., et al., JP10108681A Cathepsin K Gene Abstract. MicroPatent Bibliographic Database [Online]. [Retrieved on 1999-11-30]. Retrieved from the Internet <URL:http://www.micropat.com/htdocs/com.../nerac.00587727/JP/JP10108681.html>.					
	AZ	Askew, B., et al., "Molecular Recognition with Convergent Functional Groups. 6. Synthetic and Structural Studies With a Model Receptor for Nucleic Acid Components," <i>J. Am. Chem. Soc.</i> 111, 1082-1090 (1989).					
	AR2	Bailey, D. and Cooper, J.B., "A Structural Comparison of 21 Inhibitor Complexes of the Aspartic Proteinase from <i>Endothia parasitica</i> ," <i>Protein Sci</i> 3(11):2129-43 (1994).					
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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
AS2	Brünger, A.T., et al., "Crystallography & NMR System: A New Software Suite for Macromolecular Structure Determination," <i>Acta Crystallogr D</i> 54:905-21 (1998).		
AT2	Capell, A., et al., "The Proteolytic Fragments of the Alzheimer's Disease-Associated Presenilin-1 form Heterodimers and Occur as a 100-150-kDA Molecular Mass Complex," <i>J Biol Chem</i> 273(6):3205-11 (1998).		
AU2	Chartier-Harlin, M.C., et al., "Early-Onset Alzheimer's Disease Caused by Mutations at Codon 717 of the Beta-Amyloid Precursor Protein Gene," <i>Nature</i> 353(6347):844-6 (1991).		
AV2	Chopra, R., et al., U.S. Published Patent Application, US 2002/0055459 A1, published May 9, 2002, filing date Sept. 19, 2001.		
AW2	Citron, M., et al., "Mutation of the $\beta$ -Amyloid Precursor Protein in Familial Alzheimer's Disease Increases $\beta$ -Protein Production," <i>Nature</i> 360(6405):672-4 (1992).		
AX2	Cohen, B.A., et al., "An Artificial Cell-Cycle Inhibitor Isolated from a Combinatorial Library," <i>Proc Natl Acad Sci USA</i> 95(24): 14272-7 (1998).		
AY2	Corder, E.H., et al., "Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families," <i>Science</i> 261(5123):921-3 (1993).		
AZ2	Cowley, G., et al., "Alzheimer's, Unlocking the Mystery." <i>Newsweek</i> January 31, 2000.		
AR3	Cutfield, S.M., et al., "The Crystal Structure of a Major Secreted Aspartic Proteinase from <i>Candida albicans</i> in Complexes with Two Inhibitors," <i>Structure</i> 3(11):1261-71 (1995).		
AS3	Davies, D.R., "The Structure and Function of the Aspartic Proteinases," <i>Annu Rev Biophys Chem</i> 19:189-215 (1990).		
AT3	De Strooper, B., et al., "Deficiency of Presenilin-1 Inhibits the Normal Cleavage of Amyloid Precursor Protein," <i>Nature</i> 391(6665):387-90 (1998).		
AU3	Dealwis, C.G., et al., "X-ray Analysis at 2.0 Å Resolution of Mouse Submaxillary Renin Complexed with a Decapeptide Inhibitor CH-66, Based on the 4-16 Fragment of Rat Angiotensinogen," <i>J. Mol. Biol.</i> 236(1):342-60 (1994).		
AV3	Dunn, B.M. ed., Yamamoto, Kenji, et al., "Biological Significance and Activity Control of Cathepsin E Compared with Cathepsin D." In: <i>Structure and Function of the Aspartic Proteinases</i> , (NY: Plenum) pp. 297-306 (1991).		
EXAMINER		DATE CONSIDERED	



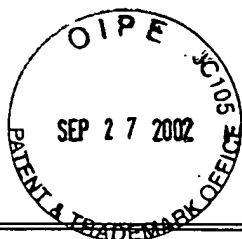
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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
	AW3	Ellington, A.D. and Szostak, J.W., "In Vitro Selection of RNA Molecules that Bind Specific Ligands," <i>Nature</i> 346(6287):818-22 (1990).	
	AX3	Ermolieff, J., et al., "Proteolytic Activation of Recombinant Pro-memapsin 2 (Pro $\beta$ -secretase) Studied with New Fluorogenic Substrates," <i>Biochemistry</i> 39(40): 12450-12456 (2000).	
	AY3	Fan, W. et al., "BACE Maps to Chromosome 11 and a BACE Homolog, BACE2, Reside in the Obligate Down Syndrome Region of Chromosome 21," <i>Science</i> 286:1255a(1999).	
	AZ3	Fields, S. and Song, O., "A Novel Genetic System to Detect Protein-Protein Interactions," <i>Nature</i> 340(6230):245-6 (1989).	
	AR4	Ghosh, A.K. and Fidanze, S., "Transition-State Mimetics for HIV Protease Inhibitors: Stereocontrolled Synthesis of Hydroxyethylene and Hydroxyethylamine Isosteres by Ester-Derived Titanium Enolate Syn and Anti-Aldol Reactions," <i>J Org. Chem.</i> 63:6146-54(1998).	
	AS4	Ghosh, A.K., et al., "Design of Potent Inhibitors for Human Brain Memapsin 2 ( $\beta$ -secretase)," <i>J. Am. Chem. Soc.</i> , 122(14): 3522-3523 (2000).	
	AT4	Glenner G.G. & Wong, C.W., "Alzheimer's Disease: Initial Report of the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein," <i>Biochem Biophys Res Commun</i> 120(3):885-90 (1984).	
	AU4	Goate, A., et al., "Segregation of a Missense Mutation in the Amyloid Precursor Protein Gene with Familial Alzheimer's Disease," <i>Nature</i> 349(6311):704-6 (1991)	
	AV4	Goldgaber, D., et al., "Characterization and Chromosomal Localization of a cDNA Encoding Brain Amyloid of Alzheimer's Disease," <i>Science</i> 235(4791): 877-80 (1987).	
	AW4	Gurney M.E., et al. U.S. Published Patent Application, US 2002/0081634 A1, published Jun. 27, 2002, filing date Apr. 5, 2001.	
	AX4	Haass, C. and De Strooper, B., "The Presenilins in Alzheimer's Disease-- Proteolysis Holds the key," <i>Science</i> 286:916-919 (1999).	
	AY4	Hong, et al., "Structure of the Protease Domain of Memapsin 2 ( $\beta$ -secretase) Complexed with Inhibitor," <i>Science</i> 290: 150-153 (2000).	
	AZ4	Hook, V.Y.H., U.S. Published Patent Application, US 2002/0072050 A1, published June 13, 2002, filing date Feb. 28, 2001.	
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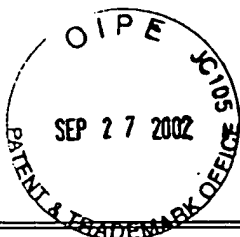
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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
AR5	James, M.N.G., <i>Aspartic Protinases, Retroviral and Cellular Enzymes</i> , Adv in Exptl Med Biol 436 (NY" Plenum) (1998).		
AS5	Jones, T.A., et al., "Improved Methods for Binding Protein Models in Electron Density Maps and the Location of Errors in these Models," <i>Acta Crystallogr A</i> 47(Pt 2):110-19(1991).		
AT5	Jorm, A.F., ed. <i>A Guide to the Understanding of Alzheimer's Disease and Related Disorders</i> (New York University Press) (1987).		
AU5	Kang, et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> 325(6106): 733-6(1987).		
AV5	Kearney, B.P. and Aweeka, F.T., "The Penetration of Anti-Infectives into the Central Nervous System" <i>Neurol. Clin.</i> 17(4):883-900 (1999).		
AW5	Kelly, D.J. and Dow, C.S., "Microbial Differentiation: The Role of Cellular Asymmetry," <i>Microbiol Sci</i> 1(9):214-9 (1984).		
AX5	Khan, A.R., et al., "Lowering the Entropic Barrier for Binding Conformationally Flexible Inhibitors to Enzymes," <i>Biochemistry</i> 37(48):16839-45 (1998).		
AY5	Knops, J., et al., "Cell-type and Amyloid Precursor Protein-type Specific Inhibition of A $\beta$ Release by Bafilomycin A1, a Selective Inhibitor of Vacuolar ATPases," [online] <i>J Biol Chem</i> 270(6):2419-22 (1995) [retrieved from the Internet <URL: <a href="http://www.jbc.org/cgi/content/full/270/6/2419">http://www.jbc.org/cgi/content/full/270/6/2419</a> > on 1/11/01.		
AZ5	Kolata, G., "Scientists Find Enzyme Linked to Alzheimer's," <i>National Science/Health. The New York Times on the Web</i> [on-line], October 22, 1999 [retrieved on 11/19/99].		
AR6	Kostka, V. <i>Aspartic Protinases and Their Inhibitor</i> (Berlin: Walter de Grueter) (1985).		
AS6	Laskowski, P.A., et al., "Procheck: a program to check the stereochemical quality of protein structures," <i>J. Appl. Cryst.</i> 26:283-291 (1993).		
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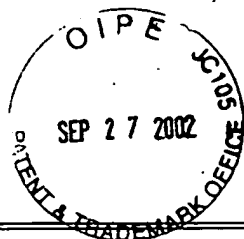
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September 24, 2002 (Use several sheets if necessary)		FILING DATE June 27, 2000	GROUP 1653
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
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AT7	McKinlay, M.A. and Rossmann, M.G., "Rational Design of Antiviral Agents," <i>Annu Rev Pharmacol Toxicol</i> 29:111-22 (1989).		
AU7	Meckelein, B., et al., "Identification of a novel serine protease-like molecule in human brain," <i>Molecular Brain Research</i> 55:181-197 (1998).		
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	AZ8	Rouvinen, J., et al., "Computer-Aided Drug Design," <i>Acta Pharmaceutica Fennica</i> 97: 159-166 (1988).	
	AR9	Rumble, B., et al., "Amyloid A4 Protein and its Precursor in Down's Syndrome and Alzheimer's Disease," <i>New Engl J Med</i> 320(22):1446-52 (1989).	
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	AR 10	Szostak, J.W. "In vitro Genetics," <i>TIBS</i> 19:89-93 (1992).	
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AV 10	Tang, J., et al., "Structural Evidence for Gene Duplication in the Evolution of the Acid Proteases," <i>Nature</i> 271(5646): 618-21 (1978).		
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